REMARKS

Reconsideration of the instant application in light of the present amendment and following remarks is respectfully requested. The present amendment is submitted with a Request for Continued Examination and is a submission under 37 CFR 1.114. Claims 1, 17, 44, and 45 are currently pending and under examination.

By the present amendment, claim 1 is amended to more specifically recite particular embodiments of the present invention. In particular, claim 1 is amended to recite that the receptor protein is non-glycosylated. Support for this amendment is provided, *e.g.*, at paragraph 85 of the application of filed. This paragraph states that a "protein," as recited in the instant claims, may be a modified amino acid and that modifications include, for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation and any other operation or modification (for example, conjugation with a labeling component). Similarly, the instant specification indicates at paragraph 109 that protein modifications, such as glycosylation "can be performed." Thus, it is clear from the instant specification that receptor proteins of the present invention may be unmodified or modified, *e.g.*, non-glycosylated or glycosylated. Applicants also note that the courts, and specifically the U.S. Court of Appeals, Federal Circuit, has ruled that 35 U.S.C. § 112 does not require that the specification contain the literal language (*ipsis verbis*) of an amendment to the claims, as long as one of skill in the art would appreciate the disclosure to contain such teachings. *See, e.g.*, *In re Wright* 866 F.2d 422 (Fed. Cir. 1989). Applicants further note that there is no *in haec verba* requirement that must be satisfied in order to meet the requirements of Section 112, but that claim features may be supported in the specification through express, implicit, or inherent disclosure. *Ralston Purina Co. v. Far-Mar-Co., Inc.,* 772 F.2d 1570, 1575 (Fed. Cir. 1985) (The requirement is met if "the disclosure relied upon *reasonably* conveys to the artisan that the inventor had possession at that time…"). Accordingly, in view of the implicit description of unmodified proteins described above, Applicants submit that the feature that the receptor protein is non-glycosylated is clearly derivable from the instant specification, and the present amendment does not introduce new matter.

It should be noted that the amendment is made without prejudice to prosecution of any subject matter described in the instant application in a related divisional, continuation or continuation-in-part application.

Rejection Under 35 U.S.C. § 103

A. The Examiner has maintained the rejection of claim 1 under 35 U.S.C. 103(a) as being allegedly obvious over Holtzman (U.S. Patent No. 5,969,123) in view of Schatz (U.S. Patent No. 5,932,433) and further in view of Tall *et al.* (U.S. Patent No. 6,756,228). The Examiner asserts that Holtzman teaches a biochip comprising a biotinylated receptor protein immobilized via a biotinylation sequence motif, wherein the receptor protein has the ability of being specifically bound by a ligand of the receptor protein. The Examiner also asserts that Schatz teaches a recombinantly expressed biotinylated receptor protein immobilized via a factor capable of specifically binding to biotin. The Examiner further asserts that Tall *et al.* teach a LOX-1 receptor immobilized to a substrate in order to detect the presence of LOX-1 activity. The Examiner asserts that it would have been obvious to perform biotinylation of the receptor protein as described in Holtzman *in vivo* instead of *in vitro* as taught by Schatz to provide a simplified biotinylation process, and that it would have been further obvious to include as the receptor protein of Holtzman in view of Schatz, a receptor protein of LOX-1 as taught by Tall *et al.*

B. The Examiner has maintained the rejection of claims 17 and 44 under 35 U.S.C. 103(a) as being allegedly obvious over Brigham-Burke *et al.* (U.S. Patent No. 5,395,587) in view of Holtzman and further in view of Schatz and Tall *et al.* The Examiner asserts that Brigham-Burke *et al.* teach a protein immobilized on a sensor chip substrate that conforms to a shape of an insertion site of a surface plasmon resonance device, and the Examiner further relies on Holtzman, Schatz and Tall *et al.*, as discussed in section A above, to allegedly render the instant claims obvious.

C. The Examiner has also maintained the rejection of claims 17 and 45 under 35 U.S.C. 103(a) as being obvious over Muramatsu (*Analytical Chemistry*, 1987;59:2760-2763) in view of Holtzman, and further in view of Schatz and Tall *et al.* The Examiner relies on

Holtzman, Schatz and Tall *et al.*, as discussed in section A above, and further asserts that Muramatsu teaches a protein immobilized on a crystal oscillator, which allegedly renders the instant claims obvious.

Applicants traverse these grounds for rejection and submit that the presently claimed subject matter satisfies the requirements of non-obviousness under 35 U.S.C. § 103(a). Applicants maintain that the instant claims are non-obvious for the reasons presented in the prior amendments, but provide the following additional comments specific to the current rejections.

With respect to the rejection outlined in section A above (and as also applied to the rejections outlined in section B and C above), Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness. *See In re Mayne*, 104 F.3d 1339 (Fed. Cir. 1997) (The USPTO has the burden of showing a *prima facie* case of obviousness). The Examiner must at a minimum demonstrate that the combined references teach or suggest all the claim features, and even assuming, *arguendo,* that the combination of references teaches each claim feature, the Examiner must provide an explicit, apparent reason to combine these features in the fashion claimed by the Applicant with a reasonable expectation of success. *See KSR v. Teleflex, Inc.,* No. 04-1350 at 4, 14 (U.S. Apr. 30, 2007) ("A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art"). Here, the cited references, alone *or in combination*, fail to teach or suggest each feature of the instant claims, and in particular fail to teach or suggest a receptor chip comprising an immobilized scavenger receptor LOX-1, wherein the receptor protein is non-glycosylated, as recited in the amended claims. In addition, the Examiner has not provided an explicit reason as to why one of skill in the art would have been motivated to combine these references to achieve the presently claimed receptor chip with any reasonable expectation of success.

Specifically, despite the non-glycosylated state of the presently claimed biotinylated LOX-1 receptor protein, which results naturally from being produced by refolding the biotinylated receptor protein expressed as an inclusion body in a bacterial host cell (as recited in claim 1), this receptor protein immobilized on a receptor chip has the ability of being specifically bound by an endogenous LOX-1 ligand with an affinity close to that of LOX-1

protein expressed on a cell surface. In this regard, Applicants submit that the cited references *in combination* fail to teach or suggest a recombinantly produced, non-glycosylated LOX-1 receptor protein having this ability, and further submit that this ability would not have been reasonably expected based upon the understanding in the art at the time the instant application was filed.

More specifically, and contrary to the expectations at the time of filing, the present application provides data indicating that the non-glycosylated LOX-1 of the present invention binds to both AcLDL and OxLDL, typical endogenous ligands, and the dissociation constant (K_D) of the non-glycosylated LOX-1 of the present invention is 10^{-11} M according to BIACORE analysis (pages 60-62). Those skilled in the art would understand such an affinity to be very high (a K_D of 10^{-11} M indicates an affinity higher than that of a typical good antibody). This value is comparable to the dissociation constant of LOX-1 expressed on a cell surface. Given the expectations at the time of filing, it is remarkably surprising that Applicants were able to produce an array comprising an immobilized, non-glycosylated LOX-1 protein able to bind to its endogenous ligands with such high affinity.

The evidence of record shows that a person of ordinary skill in the art at the time of filing would not have expected non-glycosylated LOX-1 to bind to its endogenous ligand, as recited in the instant claims. For instance, as described in detail in the prior response, it was previously known in the art that non-glycosylated LOX-1 has substantially reduced binding affinity for its endogenous ligand. On this point, Kataoka *et al.* (*Journ. Biol. Chem.*, 2000;275(9):6573-6579) teach that the affinity of non-glycosylated LOX-1 for its endogenous ligand significantly decreases as compared to glycosylated LOX-1. Kataoka *et al.*, thus, teach away from relying on non-glycosylated LOX-1 in the assay as presently claimed, since such assays typically rely on high binding affinity. Given this expectation of reduced affinity, the skilled artisan would not have reasonably expected a recombinant LOX-1 polypeptide produced according to the teachings of the cited references to specifically bind an endogenous ligand, particularly when immobilized on a chip, as presently claimed.

Moreover, as previously made of record and further to the contrary teachings of Kataoka *et al.*, the understanding in the art at the time of filing was that there were significant

technical hurdles associated with expressing and purifying post-translationally modified mammalian receptor proteins, such as LOX-1, in high amounts using a bacterial host (*see, e.g.,* page 3, lines 8-26 of the specification). The cited references do not even remotely suggest that non-glycosylated LOX-1 receptor protein can be successfully adapted to such bacterial *in vivo* biotinylation and expression protocols. Producing functional, re-folded proteins that can be identically oriented due to *in vivo* biotinylation in an amount sufficient to produce receptor chips was not previously attainable prior to the disclosure of the present application. A person of ordinary skill in the relevant art at the time of filing would, therefore, have had no reasonable expectation of success in arriving at the claimed subject matter based upon the teachings of the cited references, as these references fail to teach or in any way suggest producing a ligand binding, correctly re-folded, *in vivo* biotinylated, non-glycosylated LOX-1 receptor protein from inclusion bodies in a bacterial host. Without specific guidance in this regard, mere mention of mammalian LOX-1 immobilized on a solid surface can not render obvious the presently claimed subject matter.

Thus, even if the cited references could be combined to teach a receptor chip containing a recombinantly produced biotinylated, non-glycosylated LOX-1 protein, as asserted by the Examiner, this does not render the claimed invention obvious, since these references, as evidenced by the state of the art, would not have motivated the skilled artisan to combine their individual teachings to produce the claimed receptor chip with a reasonable expectation of success. This lack of motivation and reason to combine the teachings of the various references with a reasonable expectation of success is particularly striking, since, as evidenced by the contrary teachings of Kataoka *et al.*, the results obtained by Applicants would certainly not have been expected by a person skilled in the art. The cited references completely fail to teach a recombinantly produced, non-glycosylated LOX-1 polypeptide that specifically binds to an endogenous ligand, and, thus, fail to provide a person skilled in the art at the time of filing with any reasonable expectation of achieving the results described and claimed by Applicants. Absent the requisite motivation and reasonable expectation of success in practicing the subject matter of the instant claims, the Examiner has not established a *prima facie* case of obviousness over the same.

As previously made or record and further to the non-obviousness of the instant claims, the presently claimed receptor chip offers unexpected advantages over the teachings of the prior art. For instance, Applicants' substantial inventive efforts unexpectedly succeeded in adapting *in vivo* biotinylation and expression protocols for use with a highly post-translationally modified mammalian receptor protein, allowing non-glycosylated LOX-1 protein to be produced for functional solid phase immobilization at levels higher than previously found in the art. Moreover, the receptor chip of the instant application attains significant effects in terms of detection of extremely low concentrations of endogenous ligand, thereby achieving advantages in terms of sensitivity that would not be expected by those skilled in the art of a receptor described in Tall *et al.* was biotinylated *in vivo*, using the method described in Schatz, and employed in the invention of Holtzman.

In view of the expectation by one skilled in the art of significantly reduced binding, or even non-optimal binding, as acknowledged by the Examiner, of non-glycosylated LOX-1 to its natural ligand, the effects demonstrated by Examples 3 and 4 and Figures 3 and 4 of the instant application could not have been predictable to one of ordinary skill in the art in view of the cited references, and as such, the invention of claim 1 cannot be considered as being obvious. Particularly in light of Kataoka *et al.*, the ability of the non-glycosylated claimed receptor polypeptides, produced as recited in claim 1, to specifically bind an endogenous ligand is clearly an unexpected result that would overcome a *prima facie* case of obviousness (M.P.E.P. § 2144.09 VII).

With regard to the rejections outlined in sections B and C above, Applicants also submit that the Examiner has failed to establish a *prima facie* case of obviousness over these claims. *See In re Mayne*, 104 F.3d 1339 (Fed. Cir. 1997) (The USPTO has the burden of showing a *prima facie* case of obviousness). As described above, Holtzman, Schatz and Tall *et al.*, alone or in combination, fail to teach the unexpected high affinity of non-glycosylated LOX-1 to endogenous ligands, such as AcLDL and OxLDL, of independent claim 1 as amended. Neither Brigham-Burke *et al.* nor Muramatsu remedy the deficiencies as noted herein, as these references concededly fail to teach a biotinylated, non-glycosylated LOX-1 protein that is capable of binding its endogenous ligand with high affinity. In addition, the skilled artisan

would have had no reasonable expectation of successfully producing a receptor chip comprising a non-glycosylated LOX-1 protein having this ability. Thus, Applicants submit that the present amendments and above remarks also overcome the rejections of dependent claims 17, 44, and 45.

In view of the Remarks and Amendments provided herein, Applicants submit that claim 1 and those claims dependent therefrom satisfy the requirements of non-obviousness under 35 U.S.C. § 103 and respectfully request reconsideration and withdrawal of the Examiner's rejection.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants respectfully submit that all of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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CDL:jjl

Enclosures:
Supplemental Information Disclosure Statement Transmittal
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Cited Reference (1)

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